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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/830,669	MARLIERE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-104 and 106-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *86-102,108-115 and 118* is/are allowed.

6)☒ Claim(s) *103,107 and 119-132* is/are rejected.

7)☒ Claim(s) *104,106,116 and 117* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 5/1/2009, in which claims 133 and 134 were canceled, and claims 103, 106, 116, 123-125 and 130-132 were amended. Claims 86-104 and 106-132 are pending and under consideration.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Claim Objections

Claim 116 is objected to because of the following informalities: the phrase "wherein R_1 and R_2 represents radicals" should be replaced with the phrase "wherein R_1 and R_2 represent radicals" to improve the grammar of the claim. Claim 117 depends from claim 116 and is objected to for the same reason applied to claim 116. Appropriate correction is required.

Response to Arguments - Claim Objections

The previous objections of claims 123-125 and 130-132 have been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/1/2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 103, 107 and 119-132 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**. This rejection was made in the Office action mailed 12/1/2008 and has been rewritten to address the amendments to the claims in the reply filed 5/1/2009.

In the reply filed 5/1/2009, claim 103 was amended to limit the bacterial or yeast cell obtainable by the method of claim 86 to a cell that "comprises valyl-tRNA synthase including at least one mutation corresponding to K277Q, R223H, V276A or D230N, which correspond to K277Q, R223H, V276A or D230N of *E. coli* valyl-tRNA synthase, which allows said valyl-tRNA synthase to charge compounds that show steric resemblance to valine." The specification describes *E. coli* strains that contain one of the following mutations in the endogenous valyl-tRNA synthase gene: K277Q, R223H, V276A or D230N (e.g., pages 8, 24 and 31). At page 31, lines 23-27, the specification states, "Each one of these clones was shown to carry a different point mutation in the ValS gene, validating the selective screen as a means of diversifying the activity of valyl-tRNA synthetase in Escherichia coli." The specification does not disclose the corresponding mutations for other bacteria or yeast. The specification envisions identifying at least one mutation in an aminoacyl-tRNA synthetase gene of yeast or bacteria (e.g., page 6, lines 8-15). However, the mutations are defined relative to the corresponding wild-type gene (e.g., page 6, lines 8-15; page 6, lines 25-38) and not relative to the corresponding mutations in the *E. coli* valyl-tRNA synthetase gene. Except for the *E. coli* valyl tRNA synthetase mutations,

specific mutations are not described by the specification but would be obtained by selection of random mutations that confer the desired function. The as-filed specification provides general support for mutations in aminoacyl-tRNA synthetase genes of yeast and bacteria, and for the specific mutations in the valyl-tRNA synthetase gene of *E. coli* but does not provide support for the previously unnamed species of valyl-tRNA synthetase mutations in other bacteria or in yeast.

In the reply filed 5/1/2009, claim 125 was amended. The claim is drawn to a bacterial or yeast cell which comprises a valyl-tRNA synthase including at least one mutation corresponding to K277Q, R223H, V276A or D230N, which correspond to K277Q, R223H, V276A or D230N of *E. coli* valyl-tRNA synthase, which allows said valyl-tRNA synthase to charge compounds that show steric resemblance to valine. The specification describes *E. coli* strains that contain one of the following mutations in the endogenous valyl-tRNA synthase gene: K277Q, R223H, V276A or D230N (e.g., pages 8, 24 and 31). At page 31, lines 23-27, the specification states, "Each one of these clones was shown to carry a different point mutation in the ValS gene, validating the selective screen as a means of diversifying the activity of valyl-tRNA synthetase in Escherichia coli." The specification does not disclose the corresponding mutations for other bacteria or yeast. The specification envisions identifying at least one mutation in an aminoacyl-tRNA synthetase gene of yeast or bacteria (e.g., page 6, lines 8-15). However, the mutations are defined relative to the corresponding wild-type gene (e.g., page 6, lines 8-15; page 6, lines 25-38) and not relative to the corresponding mutations in the *E. coli* valyl-tRNA synthetase gene. Except for the *E. coli* valyl tRNA synthetase mutations, specific mutations are not described by the specification but would be obtained by selection of random mutations that confer the desired function. The as-filed specification provides general support for mutations in aminoacyl-tRNA

synthetase genes of yeast and bacteria, and for the specific mutations in the valyl-tRNA synthetase gene of *E. coli* but does not provide support for the previously unnamed species of valyl-tRNA synthetase mutations in other bacteria or in yeast.

The reply filed 8/11/2008 asserts that the claims are supported by the specification. Further, the response notes that the claims are directed to embodiments discussed in the paragraph bridging pages 4 and 5 of the Office action. The reply filed 5/1/2009 asserts that support for the claims is found at page 6, lines 8-24; however this portion of the specification describes mutations in aminoacyl-tRNA synthetase genes as compared with the sequence of the "corresponding wild type gene" and not the corresponding gene of *E. coli* valyl-tRNA synthase, as claimed. In other words, a mutant yeast aminoacyl-tRNA synthase is compared to the wild type yeast aminoacyl-tRNA synthase, not *E. coli* valyl-tRNA synthase. The original specification has been thoroughly reviewed, and no support could be found for the amendments to claim 103, and claims that depend therefrom, and new claim 125, and claims that depend therefrom. The prior Office action indicates that *E. coli* strains deposited with the CNCM are described by the present specification, and these strains contain the mutations now claimed. However, the specification does not provide explicit or implicit support for the corresponding mutations in other bacteria or yeast valyl-tRNA synthase genes.

Claim 124 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new rejection, necessitated by the amendment of claim 124 to depend from claim 86 in the reply filed 5/1/2009.

The claim is drawn to a bacterial cell or yeast cell obtainable by the method of claim 86. The method of claim 86 is drawn to the steps of (a) introducing at least one missense mutation in a target codon of a gene encoding a protein required for the growth of the bacterial or yeast cells, wherein the mutated protein synthesized from the mutated gene is not functional in the bacterial or yeast cells; (b) selecting the bacterial or yeast cells obtained in (a) in a culture medium which (1) does not contain a nutrient compensating for the loss of functionality of the mutated protein and (2) contains an unconventional amino acid which restores the functionality of said protein required for growth of the bacterial or yeast cells, said unconventional amino acid being that encoded by said target codon; and (c) culturing the bacterial yeast cells obtained in (b) in a culture medium containing said amino acid encoded by said target codon. Thus, the claims are drawn to a very large genus of bacterial and yeast cells defined by their ability to grow in a culture medium containing the amino acid encoded by a target codon that has been mutated by at least one missense mutation. The cells are defined by function and not by the compensatory mutations that allow for the growth of the cell containing the missense mutation in the essential gene, which is normally required for growth of the cell.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes *E. coli* strains deposited at the CNCM under

the Nos. I-2025, I-2026, I-2027, I-2339, I-2340, and I-2341, also referred to as strains β5366, β8144, β8146, β5479, β5485, and β5486, respectively (e.g. pages 7-9). Strain I-2025 (β5366) does not meet the structural or functional limitations of the claims in that the strain is incapable of growing without thymine or thymidine due to the absence of a mutation in any gene capable of suppressing the missense mutation in the thyA gene (e.g. Example 1). Strains I-2026 and I-2027 contain the K277Q allele of the ValS gene (e.g. page 24, lines 23-25). Strain I-2339 contains the R223H allele of the ValS gene (e.g. page 8, lines 13-24). Strain I-2340 contains the V276A allele of the ValS gene (e.g. page 8, lines 25-34). Strain I-2341 contains the D230N allele of the ValS gene (e.g. page 9, lines 7-8). Thus, each of the strains described in the instant specification is a strain of *E. coli* with a missense mutation in the ValS gene.

The claims encompass any mutant of any gene that will compensate for the loss of the essential gene product. For example, loss of an essential drug resistance marker might be compensated for by the generation of a "leaky" mutant of a protein pump on the cell surface. Thus, the rejected claims encompass a number of different mutants that do not necessarily include mutants of a valyl tRNA-synthase gene. One cannot extrapolate from the examples described in the specification, bacterial cells and yeast cells that have compensatory mutations sufficient to support the broad genus claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-*

Cath at page 1116). As discussed above, the skilled artisan cannot envision the genetic modifications conferring the claimed function, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

Given the very large genus of yeast and bacterial cells encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to genetic modifications that meet the functional limitations of the claims for a representative number of bacterial and yeast organisms, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of isolated cells. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claim 124.

Response to Arguments - 35 USC § 112

The rejection of claims 133 and 134 under 35 U.S.C. 112, second paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 5/1/2009.

The rejection of claims 103, 104, 107, 116, 117 and 119-132 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/1/2009.

The rejection of claims 133 and 134 under 35 U.S.C. 112, first paragraph, is moot in view of Applicant's cancellation of the claims in the reply filed 5/1/2009.

With respect to the rejection of claims 103, 107 and 119-132 are rejected under 35 U.S.C. 112, first paragraph (new matter), Applicant's arguments filed 5/1/2009 have been fully considered but they are not persuasive.

The response asserts that the specification at page 6, lines 8-24 provides support. This portion of the specification indicates that an aminoacyl-tRNA synthetase has at least one mutation compared with the sequence of the **corresponding wild type gene**. The gene may be from bacterial cells or yeast cells. The response asserts that this passage conveys to one skilled in the art that the mutations K277Q, R223H, V276A or D230N of *E. coli* valyl-tRNA synthetase should be transposed onto corresponding wild-type valyl-tRNA synthetases of other bacterial and yeast cells.

These arguments are not found persuasive. The specification does not convey the idea that the mutations identified in *E. coli* valyl-tRNA synthetase should be transposed onto corresponding wild-type valyl-tRNA synthetases of other bacterial and yeast cells. This is a new concept. The specification envisions the isolation of bacterial and yeast strains comprising a mutation in an aminoacyl tRNA-synthetase, where the mutation is obtained upon selection of randomly obtained mutations and is identified by comparing the sequence of the nucleic acid sequence of the gene encoding the aminoacyl-tRNA synthetase with the sequence of the wild-type gene. One of skill in the art would have understood the specification to be referring to a comparison of the sequence of the mutated aminoacyl-tRNA synthetase nucleic acid to the sequence of the unmodified copy of the same gene from the same species. The specification

does not define "wild-type" to refer to the mutated versions of *E. coli* valyl-tRNA synthetase. The term "wild-type" would have been understood to refer to the unmodified form of the gene from the same species.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

Claims 86-102, 108-115 and 118 are allowed.

Claims 104 and 106 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston
Examiner
Art Unit 1636

/JD/

/ Christopher S. F. Low /
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